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=> d his

     (FILE 'HOME' ENTERED AT 18:07:26 ON 23 MAR 2004)

     FILE 'MEDLINE' ENTERED AT 18:07:32 ON 23 MAR 2004
L1         21623 S MUSCARINIC
L2          8268 S L1 (P) ANTAGONIST?
L3          1078 S L2 AND M3
L4             0 S L3 AND (ASTHMA AND COPD AND BRADYCARDIA AND SPASM?)
L5            68 S L3 AND (STRUCTURE ACTIVITY)
L6             0 S L5 AND REVIEW?
L7             0 S L5 AND ASTHMA
L8             1 S L5 AND SPASM?
L9             0 S L5 AND TRAPAN?
L10            3 S L5 AND TROPAN?

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=> d bib abs 1-3

L10 ANSWER 1 OF 3 MEDLINE on STN
AN 1999172303 MEDLINE
DN PubMed ID: 10072477
TI **M3**/M1-Selective antimuscarinic tropinyl and piperidinyl esters.
AU Xu R; Sim M K; Go M L
CS Department of Pharmacy, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260, Singapore.
SO European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, (1999 Apr) 8 (1) 39-47. Journal code: 9317982. ISSN: 0928-0987.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199906
ED Entered STN: 19990714
Last Updated on STN: 19990714
Entered Medline: 19990629
AB The binding affinities of some tropinyl and piperidinyl esters for the submandibulary glands (**M3**/M1) and heart ventricle (M2) were determined from displacement experiments using 3H-labelled N-methylscopolamine as radioligand. The antimuscarinic activities of these esters were also evaluated on guinea pig bronchi. The esters inhibited the **M3**-mediated carbachol-induced contraction of the bronchial smooth muscle and a reasonable correlation was obtained between the binding affinities of the esters for the submandibulary glands (pKM3,M1) and their inhibitory activities (pIC50) on guinea pig bronchi. A promising compound, N-methylpiperidinyl cyclohexylphenylpropionate (NCPP) which combined good antimuscarinic activity (pA2=9.34) with a 20-fold selectivity at the **M3**/M1 receptors, was identified. Quantitative **structure-activity** relationships (QSAR) showed that the size of the ester was the main structural feature determining both binding affinity for the **M3**/M1 receptors and inhibitory activity on guinea pig bronchi. Esters with substituted acyl side chains (fewer hyperconjugable H atoms at the alpha-carbon) are generally associated with better activity and affinity.

L10 ANSWER 2 OF 3 MEDLINE on STN
AN 1998162080 MEDLINE
DN PubMed ID: 9501459
TI Synthesis, antimuscarinic activity and quantitative **structure-activity** relationship (QSAR) of tropinyl and piperidinyl esters.
AU Xu R; Sim M K; Go M L
CS Department of Pharmacy, National University of Singapore, Republic of Singapore.
SO Chemical & pharmaceutical bulletin, (1998 Feb) 46 (2) 231-41. Journal code: 0377775. ISSN: 0009-2363.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980416
Last Updated on STN: 20020917
Entered Medline: 19980408
AB A series of tropinyl and piperidinyl esters was synthesized and evaluated for inhibitory activities on the endothelial muscarinic receptors of rat (**M3**) and rabbit (M2) aorta. Some of the esters (cyclohexylphenylglycolates and cyclohexylphenylpropionates) were found to be better antimuscarinic compounds than standard M2 and **M3** inhibitors such as AFDX116 and 4-diphenylacetoxy-N-methylpiperidine (DAMP), with pKEC50 values in the range of 8-9. A few esters were found to be more selective **M3** than M2 inhibitors, but these tended to have low activities. The hydrophobic, electronic and steric characteristics of these esters were correlated with antimuscarinic activity by using appropriate parameters representing hydrophobicity (HPLC capacity factor, log kw), size (molecular volume) and electronic character (Taft's polar substituent constant sigma * and 13C chemical shift difference delta delta). Finally, 92% of the M2-inhibitory activities of the esters could be accounted for by the size and electronic character sigma * of the side chain. In contrast, the **M3**-inhibitory activities of these esters were mainly attributed to the electronic nature (sigma *, delta delta) of the side chain, with good activity being associated with electron-withdrawing groups. Visualization of the comparative molecular field analysis (CoMFA) steric and electrostatic fields provided further confirmation of the **structure-**

activity relationship (SAR) derived from traditional quantitative **structure activity** relationship (QSAR) approaches.

L10 ANSWER 3 OF 3 MEDLINE on STN
AN 92065458 MEDLINE
DN PubMed ID: 1956033
TI Synthesis, molecular modeling studies, and muscarinic receptor activity of azaprophen analogues.
AU Triggle D J; Kwon Y W; Abraham P; Pitner J B; Mascarella S W; Carroll F I
CS Research Triangle Institute, Research Triangle Park, North Carolina 27709.
NC AG-07418 (NIA)
SO Journal of medicinal chemistry, (1991 Nov) 34 (11) 3164-71.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199112
ED Entered STN: 19920124
Last Updated on STN: 19970203
Entered Medline: 19911231
AB Synthesis, radioligand binding, and pharmacologic activities of a series of **muscarinic** receptor ligands including and related to azaprophen (6-methyl-6-azabicyclo[3.2.1]octan-3 alpha-ol 2,2-diphenylpropionate, 1) have been measured to determine activity and selectivity for **muscarinic** receptor subtypes. Pharmacologic affinities of **antagonists** were determined as pA2 values for antagonism of methacholine-induced tension responses in guinea pig ileum. Binding affinities were measured by competition against [3H]QNB binding in guinea pig ileum, rat heart and brain, and m1- or **m3**-transfected Chinese hamster ovary (CHO) cells. The efficacies of **muscarinic** agonists in brain were determined by the ratio of binding affinities against [3H]QNB or [3H]NMS and [3H]oxotremorine-M ([3H]Oxo-M). Nine **muscarinic antagonists**, including azaprophen, did not discriminate significantly between the subtypes of **muscarinic** receptors. KI values for receptor binding for azaprophen (1) were between 8.81 x 10(-11) and 4.72 x 10(-10) M in ileum, heart, brain, and m1- or **m3**-transfected CHO cells. The alpha- and beta-benzilate esters 5 and 6 are as potent as azaprophen, and diphenylacetate esters 3 and 4 and N-(6)-benzyl alpha-isomer 7 are less potent than azaprophen. Significant stereoselectivity was exhibited with (+)-azaprophen being approximately 200 times more potent than the (-)-enantiomers and the 3 beta-ol isomer 2 being ca. 50 times less potent than azaprophen in all systems. A molecular modeling-molecular mechanics study was conducted to account for the difference. Putative **muscarinic** agonists (analogues and isomers of 6-methyl-6-azabicyclo[3.2.1]octan-3-ol acetate) did not discriminate **muscarinic** receptor subtypes with KI values between 2.77 x 10(-6) and 4.33 x 10(-5) M without significant stereoselectivity in the systems examined. The most active analogue was (1R,3R,5S)-6-[1(R)-phenylethyl]-6-azabicyclo[3.2.1]octan-3 alpha-ol acetate. However, efficacies of these putative agonists were in general very low.

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=> d bib abs

L8 ANSWER 1 OF 1 MEDLINE on STN
AN 95306430 MEDLINE
DN PubMed ID: 7786837
TI Muscarinic receptors and drugs in cardiovascular medicine.
AU van Zwieten P A; Doods H N
CS Department of Pharmacotherapy, Academic Medical Center, University of Amsterdam, The Netherlands.
SO Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy, (1995 Feb) 9 (1) 159-67. Ref: 63
Journal code: 8712220. ISSN: 0920-3206.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199507
ED Entered STN: 19950807
Last Updated on STN: 20020917
Entered Medline: 19950727
AB The parasympathetic system and its associated **muscarinic** receptors have been the subject of a renaissance of interest for the following two main reasons: (1) the association of endothelial **muscarinic** receptors and the nitric oxide (NO) pathway; (2) the discovery of several **muscarinic** receptor subtypes and drugs interacting with them. In the present survey modern insights into the subdivision of **muscarinic** receptors have been dealt with as the basis for a description of the **muscarinic** receptor agonists and **antagonists** thus far known. There are at least four pharmacologically defined M receptors (M1, M2, **M3**, M4) in primary tissues, and five **muscarinic** receptors have been cloned (m1, m2, **m3**, m4, m5). Selective agonists for M-receptor subtypes hardly exist, and all classical agonists (acetylcholine, carbachol, etc.) are clearly nonselective. A few selective **antagonists** for M1 (pirenzepine) and M2 receptors (AF-DX 116) have been introduced, although selective **M3** receptors are hardly available. Finally, the potential therapeutic use of M-receptor agonists (myocardial ischemia, hypertension) and **muscarinic** **antagonists** (certain forms of bradycardia, coronary **spasm**) has been critically discussed. Although only in a preliminary stage, this development appears to be promising and at least of great fundamental interest.

=> d l5 30-35 bib abs

L5 ANSWER 30 OF 68 MEDLINE on STN
AN 1998378876 MEDLINE
DN PubMed ID: 9713254
TI Development of FUB 181, a selective histamine H3-receptor antagonist of high oral in vivo potency with 4-(omega-(arylalkyloxy)alkyl)-1H-imidazole structure.
AU Stark H; Huls A; Ligneau X; Purand K; Pertz H; Arrang J M; Schwartz J C; Schunack W
CS Institut fur Pharmazie, Freie Universitat Berlin, Germany.
SO Archiv der Pharmazie, (1998 Jun) 331 (6) 211-8.
Journal code: 0330167. ISSN: 0365-6233.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
ED Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980916
AB A series of 4-(omega-(arylalkyloxy)alkyl)-1H-imidazoles and related sulphur-containing compounds have been prepared and evaluated for their histamine H3-autoreceptor **antagonist** in vitro potency in an assay on synaptosomes of rat cerebral cortex. In addition, the in vivo potency has been determined from the changes in N tau-methylhistamine levels in brain after p.o. administration to mice. Compounds with different alkyl chains and various aryl moities have been synthesized and tested to explore **structure-activity** relationships.
Within this series of novel **antagonists**, (1H-imid-azol-4-yl)methyl and 2-(1H-imidazol-4-yl)ethyl ether derivatives showed low to moderate H3-receptor **antagonist** potency, whereas the

corresponding allyl and propyl derivatives were compounds with high **antagonist** in vitro potency. Corresponding thioether or sulphoxide derivatives also showed **antagonists** activity. Additionally, some ether derivatives possessed high in vivo potency as well. The most active ether derivatives under in vivo conditions were 4-(3-(3-(4-fluorophenyl)propyloxy)propyl)-1H-imidazole (11b) and the corresponding chloro compound 11c (FUB 181) with ED50 values of 0.76 and 0.80 mg/kg, respectively. On the other hand, all compounds tested showed weak activity at histamine H1 or H2 receptors. Furthermore, the most promising ether FUB 181 exhibited low activity at adrenergic alpha 1, beta 1/2, serotonergic 5-HT2A, 5-HT3, and **muscarinic M3** receptors. Time-course investigations of FUB 181 in mice showed a rapid mode of action with the highest value 3 h after p.o. application. Thus, FUB 181 appears to block histamine H3 receptors potently and selectively.

L5 ANSWER 31 OF 68 MEDLINE on STN
AN 1998346126 MEDLINE
DN PubMed ID: 9681148
TI Synthesis and antimuscarinic activity of some ether- and thioether-bearing 1,3-dioxolanes and related sulfoxides and sulfones.
AU Malmusi L; Franchini S; Mucci A; Schenetti L; Gulini U; Marucci G; Brasili L
CS Dipartimento di Scienze Farmaceutiche, Universita degli Studi di Modena, Italy.
SO Bioorganic & medicinal chemistry, (1998 Jun) 6 (6) 825-32.
Journal code: 9413298. ISSN: 0968-0896.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
ED Entered STN: 19981008
Last Updated on STN: 19981008
Entered Medline: 19980929
AB A series of 1,3-dioxolane-based ligands, bearing ether, thioether and related sulfoxide and sulfone functionalities, were synthesised and tested as potential **muscarinic antagonists.** The compounds display moderate to low affinity for the three receptor subtypes M1-**M3**, with some of them showing a significant selectivity for the M1-**M3** over the M2 subtype.

L5 ANSWER 32 OF 68 MEDLINE on STN
AN 1998162080 MEDLINE
DN PubMed ID: 9501459
TI Synthesis, antimuscarinic activity and quantitative **structure-activity** relationship (QSAR) of tropinyl and piperidinyl esters.
AU Xu R; Sim M K; Go M L
CS Department of Pharmacy, National University of Singapore, Republic of Singapore.
SO Chemical & pharmaceutical bulletin, (1998 Feb) 46 (2) 231-41.
Journal code: 0377775. ISSN: 0009-2363.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980416
Last Updated on STN: 20020917
Entered Medline: 19980408
AB A series of tropinyl and piperidinyl esters was synthesized and evaluated for inhibitory activities on the endothelial muscarinic receptors of rat (**M3**) and rabbit (M2) aorta. Some of the esters (cyclohexylphenylglycolates and cyclohexylphenylpropionates) were found to be better antimuscarinic compounds than standard M2 and **M3** inhibitors such as AFDX116 and 4-diphenylacetoxy-N-methylpiperidine (DAMP), with pKEC50 values in the range of 8-9. A few esters were found to be more selective **M3** than M2 inhibitors, but these tended to have low activities. The hydrophobic, electronic and steric characteristics of these esters were correlated with antimuscarinic activity by using appropriate parameters representing hydrophobicity (HPLC capacity factor, log kw), size (molecular volume) and electronic character (Taft's polar substituent constant sigma * and 13C chemical shift difference delta delta). Finally, 92% of the M2-inhibitory activities of the esters could be accounted for by the size and electronic character sigma * of the side chain. In contrast, the **M3**-inhibitory activities of these esters were mainly attributed to the electronic nature (sigma *, delta delta) of the side chain, with good activity being associated with electron-withdrawing groups. Visualization of the

comparative molecular field analysis (CoMFA) steric and electrostatic fields provided further confirmation of the **structure-activity** relationship (SAR) derived from traditional quantitative **structure activity** relationship (QSAR) approaches.

L5 ANSWER 33 OF 68 MEDLINE on STN
AN 1998129889 MEDLINE
DN PubMed ID: 9468637
TI Synthesis and biological evaluation of phenylacetyl derivatives having low central nervous system permeability as potent and selective M2 **muscarinic** receptor **antagonists.**
AU Watanabe T; Kakefuda A; Tanaka A; Takizawa K; Hirano S; Shibata H; Yamagiwa Y; Yanagisawa I
CS Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Ibaraki, Japan.
SO Chemical & pharmaceutical bulletin, (1998 Jan) 46 (1) 53-68.
Journal code: 0377775. ISSN: 0009-2363.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199805
ED Entered STN: 19980520
Last Updated on STN: 20020917
Entered Medline: 19980513
AB A series of phenylacetyl derivatives containing the 5,10-dihydro-11H-dibenzo[b,e,][1,4]diazepin-11-one or 5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one skeleton was prepared and evaluated for their binding affinities to muscarinic receptors in vitro and for antagonism of bradycardia, salivation and tremor in vivo. Among them, compounds 56 and 66 had high affinity for M2 muscarinic receptors in the heart (pKi = 8.7 and 8.9, respectively) with low affinity for **M3** muscarinic receptors in the submandibular gland. A **structure-activity** relationship (SAR) study suggested that the high M2 selectivity over the **M3** muscarinic receptors of 56 may be attributed to the direction of the carboxamide carbonyl group. In in vivo studies, 56 and 66 antagonized oxotremorine-induced bradycardia in rats on both intravenous and oral administration, and their heart rate increasing effect in dogs with nocturnal bradycardia was about 3-fold greater than that of AF-DX 116. Furthermore, they had almost no influence on oxotremorine-induced tremor in mice, presenting no evidence of central transfer.

L5 ANSWER 34 OF 68 MEDLINE on STN
AN 97473114 MEDLINE
DN PubMed ID: 9331998
TI Synthesis of novel succinamide derivatives having a 5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one skeleton as potent and selective M2 **muscarinic** receptor **antagonists.** II.
AU Watanabe T; Kakefuda A; Kinoyama I; Takizawa K; Hirano S; Shibata H; Yanagisawa I
CS Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Ibaraki, Japan.
SO Chemical & pharmaceutical bulletin, (1997 Sep) 45 (9) 1458-69.
Journal code: 0377775. ISSN: 0009-2363.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971125
AB A series of succinamide derivatives containing the 5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one skeleton (6a-z) was prepared and evaluated for binding affinity to muscarinic receptors in vitro and for antagonism of bradycardia and salivation in vivo in comparison with AF-DX 116 (1a). **Structure-activity** relationships (SAR) studies in vitro indicated that the 4-(4-alkyl-1-piperazinyl)benzylamino moiety plays a crucial role in enhancing the affinity for M2 muscarinic receptors. Compound 6y, containing a 4-(4-isopropyl-1-piperazinyl)benzylmethylamino moiety, exhibited the highest affinity for M2 muscarinic receptors (pKi = 9.2), being 200 times as potent as 1a, and compound 6u, containing a 4-(4-ethyl-1-piperazinyl)benzylethylamino moiety, showed the highest selectivity for M2 over **M3** muscarinic receptors (**M3**/M2 ratio = 320). Both 6y and 6u antagonized the oxotremorine-induced bradycardia in rats after intravenous or oral administration. Oral evaluation in conscious dogs showed that the

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efficacy for increasing the heart rate was at least 3-fold greater than that of 1a.

L5 ANSWER 35 OF 68 MEDLINE on STN
AN 97399613 MEDLINE
DN PubMed ID: 9255713
TI Cholinergic modulation of electrogenic ion transport in different regions of the rat small intestine.
AU Przyborski S A; Levin R J
CS Department of Biomedical Science, University of Sheffield, Western Bank, UK.
SO Journal of pharmacy and pharmacology, (1997 Jul) 49 (7) 691-7.
Journal code: 0376363. ISSN: 0022-3573.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199712
ED Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971208
AB Acetylcholine acting via **muscarinic** receptors located in the intestinal mucosa controls ion and fluid transport. This study examined the pathway(s) by which cholinergic receptors mediate secretion in rat isolated duodenum, jejunum and ileum using the short-circuit current (Isc) as an index of electrogenic CL- secretion. Carbachol and bethanechol induced electrogenic CL- transport which was insensitive to the neural blocker tetrodotoxin, indicating their direct action on the enterocytes. Functional characterization of electrogenic secretion activated via **muscarinic** receptors on jejunal and ileal enterocytes was achieved by use of selective **muscarinic antagonists** in the presence of tetrodotoxin. In both regions the rank order of potency of these compounds (atropine > 4-diphenylacetoxy-N-piperidine methiodide (4-DAMP) > hexahydro-sila-difenidol (HHSiD) > pirenzepine > methoctramine) indicated the **M3** receptor subtype. Secretion activated by the **muscarinic** agonist 4-[[(3-chlorophenyl)amino]carbonyl]-N,N, N-trimethyl-2-butyn-1-ammonium chloride (McN-A-343) was sensitive to tetrodotoxin and pirenzepine but not to the ganglionic blocker, hexamethonium, indicating the M1 receptor subtype on post ganglionic neurons. Regional differences for bethanechol-activated secretion showed an increasing gradient in secretory capacity (Isc max) in a proximal-to-distal direction along the small intestine. Responses to McN-A-343 also showed regional differences but these were unlike those of bethanechol. These results show that cholinomimetic-induced electrogenic CL- secretion in rat isolated small intestine appears to be mediated by two dissimilar populations of **muscarinic** receptor: **M3** **muscarinic** receptors positioned on enterocytes and M1 **muscarinic** receptors sited on submucosal neurons.

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     (FILE 'HOME' ENTERED AT 15:28:32 ON 23 MAR 2004)

     FILE 'MEDLINE' ENTERED AT 15:28:41 ON 23 MAR 2004
L1          6586 S ANTICHOLINERGIC?
L2          1163 S L1 AND (ASTHMA OR COPD OR SPASMS OR MENSTRUAL PAIN OR CARDIAC
L3           122 S L2 AND REVIEW?
L4           917 S L1 (P) (ASTHMA OR COPD OR SPASMS OR MENSTRUAL PAIN OR CARDIAC
L5           110 S L4 AND REVIEW?
L6             0 S ASTHMA AND COPD AND SPASMS AND (MENSTRUAL (W) PAIN) AND CARDI
L7             0 S ASTHMA AND COPD AND SPASMS AND PAIN AND CARDIAC
L8           432 S L1 AND ASTHMA
L9            54 S L8 AND COPD
L10            1 S L9 AND SPASM
L11          187 S L1 AND PAIN
L12          623 S L1 AND (CARDIAC OR HEART)
L13           22 S L11 AND L12
L14           88 S L1 AND SPASM
L15            1 S L14 AND L13
L16            1 S L3 AND STRUCTURE
L17           18 S L3 AND ACTIVITY
L18            6 S L17 AND ASTHMA

=>
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09965766

=> d bib abs

L15 ANSWER 1 OF 1 MEDLINE on STN
AN 2000231127 MEDLINE
DN PubMed ID: 10770358
TI Esophageal pharmacology and treatment of primary motility disorders.
AU Storr M; Allescher H D
CS Department of Internal Medicine II, Technical University of Munich, Germany.
SO Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / I.S.D.E, (1999) 12 (4) 241-57. Ref: 133
Journal code: 8809160. ISSN: 1120-8694.
CY Australia
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000517
AB Swallowing is a complex mechanism based on the coordinated collaboration of tongue, pharynx and esophagus. Disturbances of this interplay or disorders of one or several of these components lead to dysphagia, non-**cardiac** chest **pain** or regurgitation. The major primary esophageal motility disorders--achalasia, diffuse esophageal **spasm**, hypercontractile esophagus ('nutcracker esophagus') and non-specific motility disorder--are of unknown etiology. Other esophageal diseases, such as cervical diverticula or gastroesophageal reflux disease, might also be caused by a primary esophageal motility disorder. Medical treatment of esophageal disorders with esophageal hyper- or dysmotility requires agents that reduce esophageal contractile force (**anticholinergic** agents, nitrates, calcium antagonists). Despite the beneficial effect of the various drugs on esophageal motility parameters, the clinical benefit of medical treatment of esophageal motility disorders is rather disappointing. Calcium channel antagonist, alone or in combination with **anticholinergics** or nitrates, can be used as a medical trial, especially in mild achalasia. However, medical therapy is clearly inferior to pneumatic balloon dilation therapy. Recently, botulinum toxin injection was suggested as a therapeutic option in achalasia patients with good results on lower esophageal sphincter pressure (LESP) and symptom scores that were similar to the results achieved by pneumatic balloon dilation. Hypercontractile esophagus shows a good manometric response to calcium channel antagonists, but only little clinical effect in terms of improvement of symptoms. Diffuse esophageal **spasm** is a relatively rare disease and few clinical studies are available. The use of calcium channel antagonists can be beneficial, at least in some patients with diffuse esophageal **spasm.** From clinical and epidemiological studies, there is some evidence of a 'psychological' component in the pathogenesis or perception of esophageal symptoms. There is some clinical benefit from centrally acting drugs such as benzodiazepines or antidepressants. With the exception of botulinum toxin for achalasia, medical therapy of primary esophageal motility disorders is rather limited and the clinical results are poor. Further understanding of esophageal pathophysiology as well as development of new receptor-selective drugs might increase our chances of a successful treatment of primary esophageal motility disorders.

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(FILE 'HOME' ENTERED AT 15:28:32 ON 23 MAR 2004)

FILE 'MEDLINE' ENTERED AT 15:28:41 ON 23 MAR 2004
L1 6586 S ANTICHOLINERGIC?
L2 1163 S L1 AND (ASTHMA OR COPD OR SPASMS OR MENSTRUAL PAIN OR CARDIAC
L3 122 S L2 AND REVIEW?
L4 917 S L1 (P) (ASTHMA OR COPD OR SPASMS OR MENSTRUAL PAIN OR CARDIAC
L5 110 S L4 AND REVIEW?
L6 0 S ASTHMA AND COPD AND SPASMS AND (MENSTRUAL (W) PAIN) AND CARDI
L7 0 S ASTHMA AND COPD AND SPASMS AND PAIN AND CARDIAC
L8 432 S L1 AND ASTHMA
L9 54 S L8 AND COPD
L10 1 S L9 AND SPASM
L11 187 S L1 AND PAIN
L12 623 S L1 AND (CARDIAC OR HEART)
L13 22 S L11 AND L12

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L14 88 S L1 AND SPASM
L15 1 S L14 AND L13

=> s l3 and structure
466497 STRUCTURE
L16 1 L3 AND STRUCTURE

=> d bib abs

L16 ANSWER 1 OF 1 MEDLINE on STN
AN 87029152 MEDLINE
DN PubMed ID: 2945691
TI Respiratory pharmacology. **Anticholinergic** agents.
AU Ziment I; Au J P
SO Clinics in chest medicine, (1986 Sep) 7 (3) 355-66. Ref: 46
Journal code: 7907612. ISSN: 0272-5231.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 198612
ED Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19861215
AB Although the **anticholinergic** agents are among the oldest of all respiratory drugs, they have been used only rarely in recent years. However, newer derivatives may have an important role in the treatment of bronchospastic diseases. The pharmacology of these interesting drugs is **reviewed**, with an emphasis on the therapeutic role of ipratropium.

=> l3 and activity
L3 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l3 and activity
1183784 ACTIVITY
L17 18 L3 AND ACTIVITY

=> l17 and asthma
L17 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l17 and asthma
81070 ASTHMA
L18 6 L17 AND ASTHMA

=> d 1-6 bib abs

L18 ANSWER 1 OF 6 MEDLINE on STN
AN 2003599336 IN-PROCESS
DN PubMed ID: 14680442
TI **Review** of cetirizine hydrochloride for the treatment of allergic disorders.
AU Portnoy Jay M; Dinakar Chitra
CS Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108, USA..
jportnoy@cmh.edu
SO Expert opinion on pharmacotherapy, (2004 Jan) 5 (1) 125-35.
Journal code: 100897346. ISSN: 1465-6566.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20031219
Last Updated on STN: 20040115
AB Cetirizine hydrochloride is an orally-active and selective histamine (H(1))-receptor antagonist. It is a second-generation antihistamine and a human metabolite of hydroxyzine. Therefore, its principal effects are mediated via selective inhibition of peripheral H(1) receptors. The antihistaminic **activity** of cetirizine has been documented in a variety of animal and human models. In vivo and ex vivo animal models have shown negligible **anticholinergic** and antiserotonergic **activity**. In clinical studies, however, dry mouth has been seen

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more commonly with cetirizine than with placebo. In vitro receptor binding studies have shown no measurable affinity for receptors other than H(1) receptors. Auto-radiographical studies with radiolabelled cetirizine in the rat have shown negligible penetration into the brain. Ex vivo experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H(1) receptors. Impairment of CNS function is comparable to other low-sedating antihistamines at the recommended dose of 10 mg/day for adults. It has anti-inflammatory properties that may play a role in **asthma** management. It does not interact with concomitantly administered medications, it has no **cardiac** adverse effects, and it does not appear to be associated with teratogenicity. Cetirizine is predominantly eliminated by the kidneys with a mean elimination half-life is 8.3 h. It is rapidly absorbed, and significant clinical inhibition of a wheal and flare response occurs in infants, children and adults within 20 min of a single oral dose and persists for 24 h. No tolerance to the wheal and flare response occurs even after 1 month of daily treatment. The clinical efficacy of cetirizine for allergic respiratory diseases has been established in numerous trials. There is evidence that cetirizine improves symptoms of urticaria. Concomitant use of cetirizine also decreases the duration and amount of topical anti-inflammatory preparations needed for the treatment of atopic dermatitis. Interestingly, several clinical studies suggest that cetirizine may be useful in the treatment and prevention of mild **asthma.**

L18 ANSWER 2 OF 6 MEDLINE on STN
AN 1999442046 MEDLINE
DN PubMed ID: 10513888
TI Circadian rhythms in the pharmacokinetics and clinical effects of beta-agonist, theophylline, and **anticholinergic** medications in the treatment of nocturnal **asthma.**
AU D'Alonzo G E; Crocetti J G; Smolensky M H
CS Temple University School of Medicine, Philadelphia, Pennsylvania 19140, USA.
SO Chronobiology international, (1999 Sep) 16 (5) 663-82. Ref: 76
Journal code: 8501362. ISSN: 0742-0528.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991130
AB Published **asthma** consensus reports now acknowledge that **asthma** is a nocturnal disease in as many as 75% of those afflicted by this medical condition. Nonetheless, the treatment of this chronic obstructive pulmonary disease in the clinic continues to be based primarily on homeostatic considerations in that it relies on long-acting bronchodilator and other therapies formulated and scheduled to ensure constant or near-constant levels of medication during the 24h. The need of **asthma** patients prone to nighttime attacks is not the same during the day and night; the therapeutic requirements of patients who experience nocturnal **asthma**, especially ones with the more severe forms of the disease, are often not satisfied by conventional medications. The therapeutic response and patient tolerance to bronchodilator medications can be improved markedly when the medications are proportioned during the 24h as a chronotherapy, that is, when more medication is delivered during nighttime sleep than daytime **activity**, as verified by numerous studies. This article **reviews** how the body's circadian rhythms influence the pharmacokinetics and effects of commonly prescribed **asthma** therapies and addresses why and how they must be taken into consideration to increase the effectiveness of **asthma** treatment.

L18 ANSWER 3 OF 6 MEDLINE on STN
AN 1999135421 MEDLINE
DN PubMed ID: 9951950
TI Second-generation antihistamines: a comparative **review.**
CM Comment in: Drugs. 1999 Jun;57(6):1033-4. PubMed ID: 10400411
AU Slater J W; Zechnich A D; Haxby D G
CS College of Pharmacy, Oregon State University, Portland, USA.
SO Drugs, (1999 Jan) 57 (1) 31-47.
Journal code: 7600076. ISSN: 0012-6667.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)

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(META-ANALYSIS)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990525
Last Updated on STN: 20000303
Entered Medline: 19990507
AB Second-generation histamine H1 receptor antagonists (antihistamines) have been developed to reduce or eliminate the sedation and **anticholinergic** adverse effects that occur with older H1 receptor antagonists. This article evaluates second-generation antihistamines, including acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, loratadine, mizolastine and terfenadine, for significant features that affect choice. In addition to their primary mechanism of antagonising histamine at the H1 receptor, these agents may act on other mediators of the allergic reaction. However, the clinical significance of **activity** beyond that mediated by histamine H1 receptor antagonism has yet to be demonstrated. Most of the agents **reviewed** are metabolised by the liver to active metabolites that play a significant role in their effect. Conditions that result in accumulation of astemizole, ebastine and terfenadine may prolong the QT interval and result in torsade de pointes. The remaining agents **reviewed** do not appear to have this risk. For allergic rhinitis, all agents are effective and the choice should be based on other factors. For urticaria, cetirizine and mizolastine demonstrate superior suppression of wheal and flare at the dosages recommended by the manufacturer. For atopic dermatitis, as adjunctive therapy to reduce pruritus, cetirizine, ketotifen and loratadine demonstrate efficacy. Although current evidence does not suggest a primary role for these agents in the management of **asthma**, it does support their use for asthmatic patients when there is coexisting allergic rhinitis, dermatitis or urticaria.

L18 ANSWER 4 OF 6 MEDLINE on STN
AN 96269360 MEDLINE
DN PubMed ID: 8673983
TI Guidelines for the emergency management of **asthma** in adults. CAEP/CTS **Asthma** Advisory Committee. Canadian Association of Emergency Physicians and the Canadian Thoracic Society.
AU Beveridge R C; Grunfeld A F; Hodder R V; Verbeek P R
CS Region 2 Hospital Corporation, Saint John, NB.
SO CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, (1996 Jul 1) 155 (1) 25-37. Ref: 167
Journal code: 9711805. ISSN: 0820-3946.
CY Canada
DT (GUIDELINE)
Journal; Article; (JOURNAL ARTICLE)
(PRACTICE GUIDELINE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199608
ED Entered STN: 19960822
Last Updated on STN: 20010529
Entered Medline: 19960809
AB OBJECTIVE: To develop a set of comprehensive, standardized evidence-based guidelines for the assessment and treatment of acute **asthma** in adults in the emergency setting. OPTIONS: The use of medications was evaluated by class, dose, route, onset of action and optimal mode of delivery. The use of objective measurements and clinical features to assess response to therapy were evaluated in relation to the decision to admit or discharge the patient or arrange for follow-up care. OUTCOMES: Control of symptoms and disease reflected in hospital admission rates, frequency of treatment failures following discharge, resolution of symptoms and improvement of spirometric test results. EVIDENCE: Previous guidelines, articles retrieved through a search of MEDLINE, emergency medical abstracts and information from members of the expert panel were **reviewed** by members of the Canadian Association of Emergency Physicians (CAEP) and the Canadian Thoracic Society. Where evidence was not available, consensus was reached by the expert panel. The resulting guidelines were **reviewed** by members of the parent organizations. VALUES: The evidence-based methods and values of the Canadian Task Force on the Periodic Health Examination were used. BENEFITS, HARMS AND COSTS: As many as 80% of the approximate 400 deaths from **asthma** each year in Canada are felt to be preventable. The use of guidelines, aggressive emergency management and consistent use of available options at discharge are expected to decrease the rates of unnecessary hospital admissions and return visits to emergency departments because of treatment

failures. Substantial decreases in costs are expected from the use of less expensive drugs, or drug delivery systems, fewer hospital admissions and earlier return to full **activity** after discharge. RECOMMENDATIONS: Beta2-agonists are the first-line therapy for the management of acute **asthma** in the emergency department (grade A recommendation). Bronchodilators should be administered by the inhaled route and titrated using objective and clinical measures of airflow limitation (grade A). Metered-dose inhalers are preferred to wet nebulizers, and a chamber (spacer device) is recommended for severe **asthma** (grade A). **Anticholinergic** therapy should be added to beta 2 agonist therapy in severe and life-threatening cases and may be considered in cases of mild to moderate **asthma** (grade A). Aminophylline is not recommended for use in the first 4 hours of therapy (grade A). Ketamine and succinylcholine are recommended for rapid sequence intubation in life-threatening cases (grade B). Adrenaline (administered subcutaneously or intravenously), salbutamol (administered intravenously) and anesthetics (inhaled) are recommended as alternatives to conventional therapy in unresponsive life-threatening cases (grade B). Severity of airflow limitation should be determined according to the forced expiratory volume at 1 second or the peak expiratory flow rate, or both, before and after treatment and at discharge (grade A). Consideration for discharge should be based on both spirometric test results and assessment of clinical risk factors for relapse (grade A). All patients should be considered candidates for systemic corticosteroid therapy at discharge (grade A). Those requiring corticosteroid therapy should be given 30 to 60 mg of prednisone orally (or equivalent) per day for 7 to 14 days; no tapering is required (grade A). Inhaled corticosteroids are an integral component of therapy and should be prescribed for all patients receiving oral corticosteroid therapy at discharge (grade A). Patients should be given a discharge treatment plan and clear instructions for follow-up care (grade C). VALIDATION: The guidelines share the same principles of those from the British Thoracic Society and the National Institutes of Health. Two specific validation initiatives have been undertaken: (a) several Canadian centres have been involved in the collection of comprehensive administrative data to assess compliance and outcome measures and (b) a survey of Canadian emergency physicians conducted to gather baseline informaton of treatment patterns, was conducted before development of the guidelines and will be repeated to re-evaluate emergency management of **asthma.**

L18 ANSWER 5 OF 6 MEDLINE on STN
AN 95270850 MEDLINE
DN PubMed ID: 7751523
TI Muscarinic receptors in human airways.
AU White M V
CS Institute for Asthma and Allergy, Washington, DC 20010, USA.
SO Journal of allergy and clinical immunology, (1995 May) 95 (5 Pt 2) 1065-8.
Ref: 36
Journal code: 1275002. ISSN: 0091-6749.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199506
ED Entered STN: 19950629
Last Updated on STN: 19980206
Entered Medline: 19950619
AB Muscarinic receptors play a double role in airway disorders, mediating an increase in mucus secretion, as well as constriction of smooth muscle. Cholinergic **activity** of the lung is more pronounced in large than in peripheral airways; in the nose parasympathetic stimulation leads to hypersecretion and vasodilation. This article **reviews** the differences in muscarinic subreceptors in the upper and lower airways and discusses the effectiveness of **anticholinergic** agents in blocking parasympathetic stimulation at these sites.

L18 ANSWER 6 OF 6 MEDLINE on STN
AN 87029152 MEDLINE
DN PubMed ID: 2945691
TI Respiratory pharmacology. **Anticholinergic** agents.
AU Ziment I; Au J P
SO Clinics in chest medicine, (1986 Sep) 7 (3) 355-66. Ref: 46
Journal code: 7907612. ISSN: 0272-5231.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

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LA English
FS Priority Journals
EM 198612
ED Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19861215
AB Although the **anticholinergic** agents are among the oldest of all respiratory drugs, they have been used only rarely in recent years. However, newer derivatives may have an important role in the treatment of bronchospastic diseases. The pharmacology of these interesting drugs is **reviewed**, with an emphasis on the therapeutic role of ipratropium.

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